REMARKS

Claims 1-7, 9-16 and 21-26 are pending in the above-identified application and stand rejected under 35 U.S.C. §112, second paragraph, and §103(a). Claims 1, 2, 5, 22, 23, 25 and 26 have been amended with this Response, and claims 4, 6, 21 and 24 have been cancelled. Reexamination and reconsideration of the claims as currently pending are respectfully requested.

I. Applicants' Invention.

The present invention is directed to methods of treating a bone defect and/or of embedding a prosthesis at a bone site. In one aspect of the invention a poorly crystalline apatitic calcium phosphate is employed in the method.

In another aspect of the invention, a paste is used for treating a bone defect, which comprises an amorphous calcium phosphate and an acidic second calcium phosphate and is converted *in vivo* at the implant site to a hardened calcium phosphate. The hardening process is associated with an endothermic reaction, whereby bone is formed at the implant site.

Lastly, kit claims for carrying out the claimed methods are included.

II. Amendment of the claims.

Claims 1, 2, 5, 22, 23, 25 and 26 have been amended. Support for the amendment

of claim 1 is found on page 20, lines 19-21, and page 21, line 1. Support for the amendment of claims 2, 22 and 25 is found on page 20, lines 1-2. Support for the amendment of claim 23 is found on page 20, lines 19-21. Claim 5 is amended to provide proper antecedent basis. Support for the amendment of claim 26 is found on page 27, lines 12-22. No new matter has been added with these amendments.

III. Rejection of the claims under 35 U.S.C. §112, second paragraph.

Claims 1-7, 9-16 and 21-26 stand rejected under 35 U.S.C. §112, second paragraph. The Examiner states that the terms "poorly crystalline apatitic calcium phosphate," "hydrated precursor paste," and "promoter" are not adequately descriptive of the "critical materials" of the invention. Examiner Action at page 2.

With this response, claim 1 now recites that the "poorly crystalline apatitic calcium phosphate" has "a calcium to phosphate ratio (Ca:P) in the range of 1.2-1.68 and characterized by an X-ray diffraction pattern similar to naturally occurring bone and substantially as shown in Figure 3c."

Applicants submit that this claim adequately describes the invention for the at least following reasons. (1) The claimed material must be a member of a class of materials that are apatitic. Apatites have a known structure and are clearly distinguished based on composition and lattice structure from other calcium phosphate materials. See, page 1, lines 19-28, of this application. (2) The compositional limits of the apatitic material are

defined because it is required to have a calcium to phosphate ratio of 1.2-1.68. (3) Lastly, the crystalline limits of the material are defined because its crystallinity is commensurate with that of natural occurring bone, and Applicants have provided a definite standard therefore by making reference to Figure 3c. It is submitted that use of the term "poorly crystalline apatitic calcium phosphate" is distinct and definite as required by §112, second paragraph, of the patent statute.

With this response, Applicants have amended claims 1 and 25, which now recite "a paste at the implant site, the paste comprising an amorphous calcium phosphate, an acidic second calcium phosphate and a physiologically acceptable fluid of an amount to provide a paste of formable or injectable consistency." Applicants submit that these claims adequately describe the invention because (1) the "hydrated precursor" is defined as a "paste" and no longer makes reference to a "promoter" (2) the paste recites known and definite components, e.g., amorphous calcium phosphate and an acidic calcium phosphate," and (2) the amount of fluid needed to provide a formable or injectable paste is not indefinite.

The amended claims now recite an "acidic calcium phosphate." The specification identifies many suitable calcium phosphates for use in combination with amorphous calcium phosphate, most of which are acidic (page 19, lines 26-29). Furthermore, the pH of most calcium phosphates is known. For example, articles by Brown and Chow (1986), and Chow *et al.* (1991) (which Applicants submit as Exhibits 1 and 2, respectively)

provide the pHs of calcium phosphates. In Table 1a of the Brown and Chow article (see p. 353), calcium phosphates are listed in increasing order of basicity. A similar list is found in Table I of the 1991 Chow article (see pp. 3-4). It is submitted that the instantly claimed paste is distinct and definite as required by §112, second paragraph, of the patent statute.

Lastly, the Examiner requests specific reaction conditions for the hardening process that "is associated with an endothermic reaction." Applicants submit that subjecting a paste having the composition as recited in the claims to *in vivo* conditions such as are found at the implant site provides the recited endothermic process. The *in vivo* site supplies all the required reaction conditions (temperature, etc.); no further clarification is required. Furthermore, it is straightforward to determine whether a process is endothermic. Endothermic processes may be readily identified using standard laboratory techniques, such as calorimetry.

For the foregoing reasons, withdrawal of the §112, second paragraph, rejection is respectfully requested.

IV. Scope and content of the cited art.

WO 94/04657 describes a porous bioglass that serves as a template for the seeding and culturing of osteoblastic cell *in vitro*. The seeded template is introduced into a host site requiring bone growth. The glass template is non-resorbable.

Constantz '610 describes a method of producing bone-like materials that includes combining a phosphoric acid source, a calcium phosphate and water to form a paste and immediately ("0.5-5 min, and usually not more than about 2 minutes;" col. 5, l. 27-30) introducing the paste into the appropriate site where it hardens.

WO 94/02412 describes a method of making bone *in vivo* that includes introducing an amorphous calcium phosphate containing a crystallization inhibitor to the selected site, whereby the crystallization inhibitor is leached slowly, e.g., over days (page 3, lines 7-20) from the material and the material is converted thereby to bone mineral.

Fukase et al. investigate the setting reactions of a self-hardening calcium phosphate cement prepared from tetracalcium phosphate and anhydrous dicalcium phosphate. The reaction product was a hydroxyapatite consisting "primarily of small rod-like crystals and some platy crystals" (Abstract, page 1852).

Rey describes bioresorbable poorly crystalline apatites analogous to bone mineral. The product calcium phosphate is obtained by slow hardening of a gel or slurry by slow dehydration accompanied by extensive shrinkage. Such a process is neither possible nor desirable *in vivo*.

V. Rejection of the claims under 35 U.S.C. §103(a).

Claims 1-7, 9-16 and 21-26 stand rejected as being unpatentable over WO 94/04657 or Constanz 4,880, 610 or WO 94/02412, each taken alone or in view of Rey *et*

al., Symposium Abstract (1993) ["Rey"] or Fukase et al., J. Dent Res. (1990). The Examiner asserts that it would have been obvious to apply the setting materials of the instant claims in view of the *in vivo* techniques described in the primary references. Further, the Examiner states that the claimed compositions do not exhibit improved working properties and thus are equivalent to the prior art examples. See, Paper No. 28, page 2. Applicants respectfully traverse the rejection.

Applicants point out that claims 1 and 2 differ from each other in several important aspects. In particular, claim 1 is directed to the use of a product poorly crystalline apatitic calcium phosphate in the claimed method, whereas claim 2 uses a reactive paste (hence the original use of the term "precursor"), which may or may not form a poorly crystalline apatitic calcium phosphate as the hardened product. Due to this important distinction, the relevance of the cited art to the different claims will be considered separately.

(A) With respect to claims 2, 25 and 26 and those dependent thereon.

Claims 2 and 25 are directed to a method of treating a bone defect by applying a paste including amorphous calcium phosphate, an acidic calcium phosphate in a physiologically acceptable liquid to a bone site (or a prosthesis in claim 25) and effecting *in vivo* conversion of the paste into a hardened product in an endothermic process. Claim 26 is directed to a kit for a prosthetic device including a prosthesis, a powder including amorphous calcium phosphate and an acidic calcium phosphate, and a physiologically acceptable fluid.

The Examiner relies upon any one of the primary references to teach the claimed *in vivo* method of bone formation. WO 94/04657 discloses an *in vitro* method of cell seeding on a non-bioresorbable template, and thus is not relevant to the invention. Applicants admit that both Constantz '610 and WO 94/02412 describe an *in vivo* technique in which a calcium phosphate paste is applied to a site requiring bone formation.

The Examiner relies upon the secondary references of Fukase or Rey to suggest the claimed setting materials. According to the Examiner's reasoning, it would have been obvious to substitute the prior art materials with the claimed paste, since the claimed materials "make use of known setting reactions of calcium phosphate" (Examiner Action at page 2). Applicants respectfully disagree.

Firstly, the claimed paste has a composition that is not disclosed or suggested by either Fukase et al. or Rey. Fukase et al. discloses a paste containing tetracalcium phosphate (TTCP) and anhydrous dicalcium phosphate (DCPA). Fukase et al. makes no mention of alternative reaction conditions or reagents. Rey uses a calcium phosphate gel of undisclosed composition. Neither reference teaches or suggests an amorphous calcium phosphate-containing cement, particularly in combination with an acidic calcium phosphate. Applicants submit that the use of an amorphous calcium phosphate in the recited paste leads to new, non-obvious (and advantageous) result, namely, a setting calcium phosphate cement in which setting is associated with an endothermic reaction.

Secondly, "known setting reactions of calcium phosphate" are not being employed in the claimed methods. Applicants have stated, and the Examiner has not disagreed, that the claimed reaction proceeds via an endothermic process. says assoc. w/

In contrast, the prior art method of Fukase et al. is exothermic.

In support of Applicant's assertion that the reaction of Fukase et al. is exothermic, Applicants enclose articles by P.W. Brown and M. Fulmer (1991) entitled "Kinetics of Hydroxyapatite Formation at Low Temperature" and Driessens et al. entitled "Calcium Phosphate Bone Cements," excerpted from *Encyclopedic Handbook of Biomaterials and Bioengineering. Part B. Applications* (1995), as Exhibits 3 and 4, respectively.

Brown and Fulmer conducted calorimetric studies of the reaction of dicalcium phosphate (DCP) and tetracalcium phosphate (TTCP), which are the same components as the Fukase et al. cement. They measured heat evolution for the reaction, which meets the criteria for an exothermic reaction. See, Figure 14, page 938, of Exhibit 1.

Driessens et al. confirm the exothermic nature of the reaction, stating "Brown and Fulmer measure an exothermic effect in the reaction of TTCP and DCP mixtures in a PHA [precipitated hydroxyapatite] cement" (page 866, Exhibit 2). Driessens also report temperature increases in the reaction of a large number of setting calcium phosphate cements (see Table 8, at page 864) and, in fact, indicates that all the calcium phosphate cements reviewed in his article are exothermic.

In summary, Fukase et al. disclose an exothermically setting cement, which is a

different in setting reaction and in composition than that of the claimed invention. Fukase et al. makes no mention of alternative reaction conditions or reagents. Thus, there is no motivation *based on the teachings of any of the prior art references*, which do not teach amorphous calcium phosphate of endothermically-associated setting reactions, to modify the Fukase et al. paste in the manner recited by the instant claims.

Turning now to the Rey reference, Rey does not disclose a setting reaction for calcium phosphate that is compatible with *in vivo* techniques. Rey teaches the use of a calcium phosphate gel of unspecified composition and having a much lower solids content than the claimed paste. The gel dries slowly, accompanied by extensive shrinking, to produce a hardened product. There is nothing in the teaching of Rey not in the long drying times, or the low solids content, or the extensive shrinking that would lead one to use the Rey gel material in a bone site. Thus, there is no rational motive to combine Rey with any of the primary references.

In conclusion, there is simply nothing in either Fukase et al. or Rey, either alone or in combination, that would suggest the desirability of a hardenable calcium phosphate paste containing amorphous calcium phosphate and an acidic calcium phosphate, or that would suggest the use of the paste in an endothermic process in the treatment of bone defects.

(B) With respect to claim 1 and those dependent thereon.

Claim 1 is directed to a method of treating a bone defect including introducing a

strongly resorbing, poorly crystalline apatitic calcium phosphate to the bone defect site, whereby the material is resorbed and bone is formed at the site. The Examiner relies upon any one of the primary references to teach the claimed *in vivo* method of bone formation. WO 94/04657 discloses an *in vitro* method of cell seeding on a non-bioresorbable template, and thus is not relevant to the invention. Applicants admit that both Constantz '610 and WO 94/02412 describe an *in vivo* technique in which a calcium phosphate paste is applied to a site requiring bone formation.

The Examiner relies upon the secondary references of Fukase or Rey to suggest the claimed setting materials. According to the Examiner's reasoning, it would have been obvious to substitute the prior art materials with the claimed materials, since the claimed materials "make use of known setting reactions of calcium phosphate" (Examiner Action (7/20/00), page 2). Applicants respectfully disagree.

Applicants do not dispute that the prior art in general has prepared apatitic calcium phosphate compositions of low crystallinity. Applicants submit, however, that there has been no teaching or suggestion of a low crystallinity apatitic calcium phosphate possessing the claimed bioresorbability and bone ingrowth properties that make it especially desirable and useful in the treatment of bone defects.

Fukase et al. does not teach the use of a poorly crystalline apatitic calcium phosphate. In the summary of the invention, the investigators state that the product apatite "consisted primarily of small rod-like crystals and some platy crystals" that is, a

crystalline hydroxyapatite. This is further substantiated with reference to Figure 2, which shows the X-ray diffraction pattern (XRD) of the product calcium phosphate. Although there is some broadening of the peaks over time, an indication of loss of crystallinity, the peaks in the final product are still sharp and in no way approximate the broad featureless features of the claimed poorly crystalline material, as shown in Figure 3c of the instant invention. Nor is there a suggestion of the desirability of a less crystalline material or a description of a method to obtain such a product.

Even if Fukase et al. did teach a poorly crystalline apatitic (PCA) calcium phosphate, the reference does not teach "introducing a...(PCA) calcium phosphate paste at the implant site," as recited in claim 1. Fukase et al. investigates the reaction setting times and compressive strengths of samples on the laboratory bench and suggest the use of "CPC" (calcium phosphate cement) in an implant device (page 1852). CPC is defined as a cement having tetracalcium phosphate and dicalcium phosphate dihydrate or anhydrous as its major components. Thus, a reactive paste made up of hydroxyapatite reagents, i.e., materials that react together to form hydroxyapatite, is introduced at the reaction site, and not the reacted product.

Turning now to Rey, the reference teaches that bioresorbable calcium phosphates may be used as a support for bioactive molecules, which can be progressively released as the calcium phosphate is resorbed. Rey then goes on to describe a poorly crystalline apatite having high specific surface area. Rey provides no suggestion that its poorly

crystalline apatite would promote bone ingrowth and therefore there is no teaching of using the material in sites where bone ingrowth is desirable. There is no teaching or suggestion of a calcium phosphate material having rapid bioresorbability, coupled with bone ingrowth at an implant site.

In summary, the Examiner cites references that do not disclose or suggest a poorly crystalline product, or that do not suggest their use in the manner of the claimed invention. There is no teaching or suggestion in any of these references to use a highly bioresorbable PCA calcium phosphate at a bone defect site, with the subsequent replacement of the material by bone.

The Examiner may suggest that references that disclose the existence of a poorly crystalline apatitic calcium phosphate render the claimed invention obvious. Applicants respectfully disagree. Without a showing of the recited desirable properties in the prior art material (and none of the materials are shown to be capable of bone ingrowth and/or the claimed bioresorbability), the mere existence of a poorly crystalline apatitic calcium phosphate does not render obvious its use in the treatment of bone defects, absent a showing that those materials possess some properties making them desirable for such a use.

For the foregoing reasons, it is respectfully requested that the rejection be withdrawn.

VI. Additional comments.

Applicant notes that the Examiner's Action was mailed to the incorrect address. Effective immediately, please address all communication in this application to:

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Enclosed is a petition to extend the period for replying for three months, to and including January 22, 2001, because January 20 falls on a Saturday. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: January 22, 2001

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